Steroidal Sapogenins. XXXIV. Preparation of 3-Desoxysapogenins (20α- and 20β-Series)[2,3]

Desoxysarsasapogenin (I), desoxysmilagenin (II) and desoxytigogenin (III) were prepared by Wolff–Kishner reduction of the corresponding 3-ketones. Desoxyhecogenin (IV) was made by mild Clemmensen reduction of hecogenone. A preferable procedure applicable to all saturated members of the 20α-series involved $LiAlH_4$ reduction of the corresponding 3-tosylates. The unsaturated 20α-sapogenins, desoxydiosgenin (V) and desoxyyamogenin (VI), were prepared by converting the corresponding 3-tosylates to iodo derivatives which in turn were reduced with zinc–acetic acid.

Some of the saturated members of the 20β(20-iso)-series could be prepared by Wolff–Kishner reduction of the corresponding 3-ketones. A more general procedure applicable to saturated and unsaturated 20β-desoxysapogenins involved formation of the desoxypseudosapogenin from the corresponding 20α-series, followed by isomerization in methanol–acetic acid.

In continuation of our previous studies of the steroidal sapogenin side chain,[4a,b,c,d] it was necessary that we prepare and determine the physical properties of the various 20α,25D- or 25L-3-desoxysapogenins and their 20β-analogs. Some of the compounds in the 20α-series were previously prepared by Marker and his co-workers.[5a,b,c] Their yields were low and the physical properties incompletely presented.

The primary intermediates for the preparation of 3-desoxysapogenins were the corresponding 3-hydroxy analogs. Figure 1 outlines the methods used. Initially attempts were made to prepare 3-halogen derivatives using phosphorus tri- and pentahalides or thionyl chloride prior to reduction. This route was unsuccessful because of the attack of the reagents on the sapogenin side chain.[6] Desoxysarsasapogenin (I), desoxysmilagenin (II) and desoxytigogenin (III), were prepared by CrO_3–acetic acid oxidation of the corresponding 3β-hydroxy analogs to give the 3-ketones. These were then reduced to the hydrocarbons by the Huang-Minlon[7] modification of the Wolff–Kishner reduction. A preferable procedure involved preparation

(1) A laboratory of the Eastern Utilization Research Branch, Agricultural Research Service, United States Department of Agriculture. Article not copyrighted.

(2) Paper XXXIII, E. S. Rothman and M. E. Wall, This Journal, 78, 1744 (1956).

(3) Presented in part at Fifth Meeting-in-miniature, Philadelphia Section, American Chemical Society, January 29, 1953.

(4) (a) M. E. Wall, C. R. Eddy and S. Serota, This Journal, 76, 2849 (1954); (b) M. E. Wall and S. Serota, *ibid.*, 76, 2850 (1954); (c) M. E. Wall, S. Serota and C. R. Eddy, *ibid.*, 77, 1230 (1955); (d) M. E. Wall, S. Serota and L. P. Witnauer, *ibid.*, 77, 3086 (1955).

(5) (a) R. E. Marker and E. Rohrmann, *ibid.*, 61, 846, 1284 (1939); (b) R. E. Marker and D. L. Turner, *ibid.*, 63, 767 (1941); (c) R. E. Marker, *et al.*, *ibid.*, 69, 2167 (1947); *cf.* p. 2180.

(6) For a similar example *cf.* C. Djerassi, H. J. Ringold and G. Rosenkranz, *ibid.*, 73, 5513 (1951).

(7) Huang-Minlon, *ibid.*, 71, 3301 (1949).

of the 3-tosylates followed by $LiAlH_4$ reduction[8] in 80–90% over-all yield.

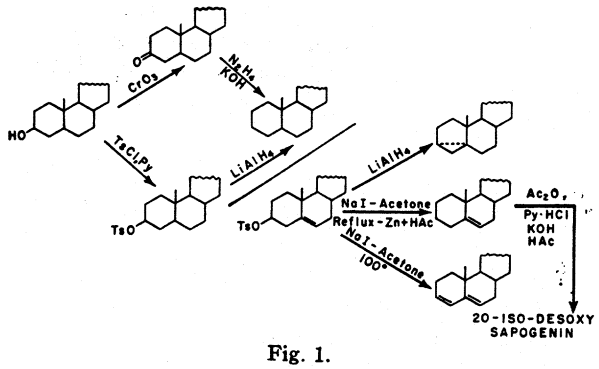

Fig. 1.

Hecogenin was converted to 3-desoxyhecogenin (IV) by two routes: (a) CrO_3 oxidation to the 3,12-diketone, hecogenone, followed by selective reduction of the 3-ketone by mild Clemmensen treatment[5c]; (b) preferable was a method involving the usual tosylation and $LiAlH_4$ reduction to give the 12-hydroxydesoxyrockogenin followed by CrO_3–pyridine oxidation to give IV in 75% over-all yield.

To prepare desoxydiosgenin (V) and desoxyyamogenin (VI), it was again necessary to prepare the 3-tosylates. Lithium aluminum hydride reduction of diosgenyl tosylate gave a mixture consisting of minor proportions of V and the conjugated $\Delta^{3,5}$-desoxydiosgenin (VII) along with the major product 3,5-cyclodesoxydiosgenin (VIII). The assignment of structure of VIII was based on analogy with the similar $LiAlH_4$ reduction of cholesteryl tosylate, which gave in part 3,5-cyclocholestane.[8] Moreover, VIII gave correct C and H values; the infrared spectrum showed absence of hydroxyl and Δ^5-unsaturation along with the typical "22α" (= 25D) "fingerprint" spectrum. Finally, the molecular rotation data were in excellent agreement with the assigned structure.[9]

Treatment of diosgenyl tosylate in acetone solution with sodium iodide at reflux gave diosgenyl iodide and unreacted tosylate. The two could be easily separated due to the high solubility of the iodide. Treatment of the latter with zinc–acetic acid gave the desired compound V. Proof of structure was obtained by hydrogenation to the known desoxytigogenin; from the infrared spectrum, which showed absence of hydroxyl, presence of Δ^5-unsaturation and typical "22α" (=25D) bands; and from the optical rotation data which were in good agreement for a Δ^5-bond.[10]

The diene $\Delta^{3,5}$-desoxydiosgenin (VII) was obtained as the sole product on treatment of diosgenyl tosylate with sodium iodide in acetone at 100°. Proof of the structure was based on hydrogenation to the known desoxytigogenin, ultraviolet absorption[11] and optical rotation values.[12] Desoxyyamogenin (VI) was prepared in the same manner as desoxydiosgenin. Structural proof was based on analogy with the previous preparation of V, proper C and H values, infrared spectrum showing absence of hydroxyl, presence of Δ^5-unsaturation and typical "22b" (= 25L) "fingerprint" bands, and finally conversion of VI to V by prolonged refluxing with hydrochloric acid.

The saturated 20-iso-3-desoxysapogenins were prepared by Wolff–Kishner reduction of the corresponding 20-iso-3-ketones.[4c] In this manner 20-isodesoxysarsasapogenin (IX), 20-isodesoxysmilagenin (X) and 20-isotigogenin (XI) were prepared. The yields were low, due probably to the instability of the 20-isosapogenin side chain.[4d] Structural proof for compounds IX, X and XI was based on proper C and H values, infrared spectrum showing absence of hydroxyl and typical 20β,25D- or 20β,25L-bands,[4c] and conversion to the respective 20α-desoxysapogenins on reflux with hydrochloric acid.

Attempts to use the tosylation and $LiAlH_4$ reduction sequence, which had been successful in the 20α-series, failed. Thus 20-isotigogenin[13] on treatment with tosyl chloride in pyridine at room temperature followed by $LiAlH_4$ reduction of the crude tosylates gave a crystalline compound which we have reason to believe was the hydrocarbon prototype of pseudotigogenin, *i.e.*, 16,22-epoxy-20(22)-cholestene (XII).[14,15]

An alternative procedure applicable to preparation of both saturated and unsaturated 20-isodesoxysapogenins involved preparation of the appropriate 20α-desoxysapogenin. The latter was then converted to the 3-desoxypseudosapogenin 26 acetate which on alkaline hydrolysis and treatment with methanol–acetic acid gave the corresponding 20β-desoxysapogenin. In this manner 20-isodesoxydiosgenin (XII) and 20-isodesoxyyamogenin (XIV) were prepared in 25% over-all yield. Structure proof of XII and XIV was established in the same manner as described above for the saturated compounds.

Experimental

Melting points were determined with a Kofler micro melting point apparatus, optical rotations were in $CHCl_3$, unless otherwise stated, 4-dec. tube, concentration approximately 8.33 mg. per ml., infrared spectra were obtained with a Perkin–Elmer model 21 instrument in CS_2 solution, concentration 10 g. per liter.

3-Desoxysarsasapogenin (20α,22a,25L-Spirostane) (I).—Ten grams of sarsasapogenin were dissolved in 50 ml. of chloroform and the solution cooled to 15°. A solution of

(8) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949).

(9) M_D 3,5-cyclocholestane[8] − M_D cholesterol = +443; M_D 3,5-cyclodesoxydiosgenin − M_D diosgenin = +424.

(10) D. H. R. Barton and W. Klyne, *Chemistry and Industry*, 755 (1948), find $\Delta\epsilon$ = −298 for a 5,6-double bond. Our experimental value was −246. Barton and Klyne calculations for other locations of the double bond give greatly different values, thus ruling out any possibility of bond migration during preparation of V.

(11) Found for VII, λ228, 234.5, 243, $\epsilon_{M.S}$ 20,500. These values were in close agreement for $\Delta^{3,5}$-dienes from data compiled by L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

(12) Barton and Klyne[10] gave −549, whereas Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publ. Corp., New York, N. Y., 1949, p. 210, gave −363 as values for the molecular contribution of the $\Delta^{3,5}$-system. Our experimental value was −379.

(13) M. E. Wall and H. A. Walens, THIS JOURNAL, **77**, 5661 (1955).

(14) The evidence for this structure was based on the infrared spectra which showed absence of hydroxyl and of the complex spiroketal bands and presence of the typical pseudosapogenin $\Delta^{20(22)}$-bond at 1687 cm.$^{-1}$ (Hayden, Smeltzer and Scheer, *Anal. Chem.*, **26**, 550 (1954)). This structure was confirmed by a positive blue color test (Rothman, Wall and Cooper, THIS JOURNAL, **75**, 6325 (1953)).

(15) Presumably 20-isotigogenin was converted to 16,22-epoxy-20(22)-cholestene-3β,26-diol 3,26-ditosylate which was then reduced to XII (*cf.* Scheer, Kostic and Mosettig, *ibid.*, **77**, 641 (1955)).

5.0 g. of CrO_3 in 30 ml. of 90% acetic acid was cooled to 15° and added dropwise to the sarsasapogenin solution with vigorous agitation. The temperature was allowed to rise to 25° and the oxidation mixture allowed to stand 1 hour. After dilution with water, the crude sarsasapogenone was extracted with chloroform, the solution dried over anhydrous sodium sulfate and the solvent evaporated. A small sample of sarsasapogenone was purified by crystallization from acetone and then ethyl acetate, as plates, m.p. 222–223° (lit.[16] m.p. 226°), $[\alpha]^{25}D$ −70°, $\bar{\nu}_{max}$ 1710 cm.$^{-1}$.

The crude sarsasapogenone without further purification was taken up in a mixture of 80 ml. of diethylene glycol and 500 ml. of ethanol to which were added 40 ml. of hydrazine hydrate and 8.0 g. of sodium hydroxide. The mixture was refluxed 0.5 hour and volatiles boiling under 190° removed. After addition of 80 ml. of diethylene glycol, the mixture was heated two hours at 190°. Benzene extraction followed by chromatography on Florisil gave 5.8 g. of product. Crystallization from ethyl acetate gave 4.5 g. (47% yield based on sarsasapogenin) of I, plates, m.p. 218–219° (lit.[5a] m.p. 214–216°), $[\alpha]^{25}D$ −73°.

3-Desoxysmilagenin (20α,22a,25D-spirostane) (II) was prepared by oxidation of smilagenin as above to give smilagenone as needles from acetone, m.p. 188° (lit.[5a] m.p. 188.5°), $[\alpha]^{25}D$ −60°, $\bar{\nu}_{max}$ 1715 cm.$^{-1}$. Wolff–Kishner reduction gave II, plates from methanol, m.p. 135–136° (lit.[5a] m.p. 140°), $[\alpha]^{25}D$ −71°.

3-Desoxytigogenin (5a,20α,22a,25D-Spirostane) (III).—Similar treatment of tigogenin gave tigogenone, m.p. 203–205° (lit.[17] m.p. 202–205°), $[\alpha]^{25}D$ −53°. $\bar{\nu}_{max}$ 1712 cm.$^{-1}$. Wolff–Kishner reduction gave III, plates from acetone, m.p. 174–175° (lit.[5b] m.p. 173°), $[\alpha]^{25}D$ −74°.

3-Desoxyhecogenin (5a-20α,22a,25D-Spirostane-12-one (IV).—Similar oxidation of hecogenin gave hecogenone as plates from ether, m.p. 237–240° (lit.[5c] gives 237–240°), $[\alpha]^{25}D$ +1.5°, $\bar{\nu}_{max}$ 1712 cm.$^{-1}$. Clemmensen reduction of hecogenone as described by Marker, *et al.*,[5c] gave desoxyhecogenin (35% yield from hecogenin) as plates from acetone, m.p. 198–199° (lit.[5c] gives 196–198°), $[\alpha]^{25}D$ +0.5°, $\bar{\nu}_{max}$ 1712 cm.$^{-1}$.

Preparation of Sapogenyl 3-Tosylates.—Although these intermediates were often used without extensive purification, a number were isolated and their properties determined. The preparation of diosgenyl 3-tosylate was typical: 20 g. of diosgenin was dissolved in 50 ml. of reagent grade pyridine with warming. On cooling, 20.0 g. of *p*-toluenesulfonyl chloride was added with shaking until all solids were dissolved. After standing overnight at room temperature, the tosyl chloride was decomposed by addition of water. The usual ether extraction,[4c] followed by concentration and crystallization from ether, gave 18.0 g. of diosgenyl tosylate, m.p. 166°, $[\alpha]^{25}D$ −98°, typical tosyl bands in infrared at 1252, 943, 813 and 668 cm.$^{-1}$.

Anal. Calcd. for $C_{34}H_{48}SO_5$: C, 71.88; H, 8.51. Found: C, 71.70; H, 8.57.

Similarly, hecogenyl tosylate was obtained as plates from acetone, m.p. 192–193°, $[\alpha]^{25}D$ −14°; $\bar{\nu}_{max}$ 1255, 948, 812, 671 cm.$^{-1}$. *Anal.* Calcd. for $C_{34}H_{48}SO_6$: C, 69.84; H, 8.27. Found: C, 69.43; H, 8.62.

Tigogenyl tosylate was obtained as rectangles from ether, m.p. 173°, $[\alpha]^{25}D$ −58°, $\bar{\nu}_{max}$ 1255, 810, 670 cm.$^{-1}$. *Anal.* Calcd. for $C_{34}H_{50}SO_5$: C, 71.55; H, 8.83. Found: C, 71.44; H, 8.79.

Sarsasapogenyl tosylate was obtained as plates from methanol, m.p. 139–140°, $[\alpha]^{25}D$ −55°; $\bar{\nu}_{max}$ 1295, 1282, 816, 685 cm.$^{-1}$. *Anal.* Calcd. for $C_{34}H_{50}SO_5$: C, 71.55; H, 8.83. Found: C, 71.58; H, 9.00.

Yamogenyl tosylate was obtained as plates from ether, m.p. 167°, $[\alpha]^{25}D$ −109°. *Anal.* Calcd. for $C_{34}H_{48}SO_5$: C, 71.88; H, 8.51. Found: C, 71.51; H, 8.55.

Lithium Aluminum Hydride Reduction of Tosylates.—The reduction of the tosylates of the saturated sapogenins proceeded almost quantitatively to give the desired desoxysapogenins. In a typical experiment 2.0 g. of tigogenyl tosylate was dissolved in 150 ml. of dry ether. The ether solution was added dropwise to a refluxing suspension of 2.0 g. of $LiAlH_4$ in 200 ml. of ether. Refluxing with vigorous stirring was continued for 5 hours. After cautious decomposition with water, hydrochloric acid was added until two distinct, clear layers were obtained. The ether layer was dried and concentrated, yield 1.78 g. of desoxytigogenin, m.p. 170–175°, infrared spectra identical to an authentic specimen.

3-Desoxydiosgenin (5-20α,22a,25D-Spirostene) (V).—Five grams of diosgenyl tosylate was dissolved in 130 ml. of dry acetone to which was added 10.0 g. of sodium iodide. After refluxing 5 hours, the solution was diluted with water and given the usual ether work-up. The residue, after removal of solvent, was triturated with low boiling petroleum ether. The insoluble residue, 1.25 g., was unchanged tosylate. The filtrate was concentrated to dryness and the residue refluxed with acetic acid (200 ml.) and 20 g. of zinc dust. Filtration, dilution of the filtrate with water and ether extraction gave 2.0 g. of V. The analytical sample gave plates from ethanol, m.p. 194–195°, $[\alpha]^{25}D$ −136°; the infrared spectrum showed typical 24D spectra, 979(s), 919(w), 898(s) cm.$^{-1}$ and Δ^5-unsaturation, 828 cm.$^{-1}$(w). *Anal.* Calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.49; H, 10.72.

Catalytic hydrogenation of V with PtO_2 in ether containing 5% acetic acid at 3 atmospheres pressure for 5 hours gave desoxytigogenin, m.p. 172–174°.

Desoxyyamogenin (5-20α,22a,25L-Spirostene) (VI).—VI was prepared from yamogenyl tosylate in the same manner as V, plates from methanol, m.p. 192°, $[\alpha]^{25}D$ −143°; infrared spectrum shows typical 25L-bands. *Anal.* Calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.24; H, 10.57.

$\Delta^{3,5}$-Desoxydiosgenin (3,5-20α,22a,25D-Spirostadiene) (VII).—One gram of diosgenyl tosylate was dissolved in 40 ml. of acetone with heating and 2.0 g. of sodium iodide added. The solution was heated in a sealed tube at 100° for 5 hours. Free iodine was present after the reaction. The acetone solution was poured into a 5% aqueous sodium thiosulfate solution. After the usual ether work-up, 0.45 g. of product, m.p. 155–160°, was obtained. On recrystallization from acetone the product had m.p. 164°, $[\alpha]^{25}D$ −175, λ_{max} (methanol) 228, 234, 243 mμ, log ϵ_{234} 4.33; infrared spectrum shows typical 25D-bands, 979(s), 917(w), 895(s) and 863(w) cm.$^{-1}$. *Anal.* Calcd. for $C_{27}H_{40}O_2$: C, 81.76; H, 10.17. Found: C, 81.31; H, 10.03. Catalytic hydrogenation of VII as described for V gave desoxytigogenin.

3,5-Cyclodesoxydiosgenin (3,5-Cyclo-20α,22a,25D-spirostane) (VIII).—Lithium aluminum hydride reduction of 6.0 g. of diosgenyl tosylate as described previously gave a product which after several crystallizations from methanol had a m.p. range 125–175°. Ultraviolet assay showed presence of *ca.* 3% diene. Crystallization from ethyl acetate gave 0.7 g. of desoxydiosgenin (V). From the soluble residues were obtained 3.5 g. of VIII as plates from ethyl acetate, m.p. 138–139°, $[\alpha]^{25}D$ −28°; infrared spectrum shows absence of bands in 3600 and 838 cm.$^{-1}$ region (no OH or Δ^5-unsaturation) and typical 25D-bands. *Anal.* Calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.41; H, 10.75.

20-Isodesoxysarsasapogenin (20β,22b,25L-Spirostane) (IX).—Wolff–Kishner reduction of 0.75 g. of 20-isosarsasapogenone[4c] gave IX, 0.16 g., needles from methanol, m.p. 131–132°, $[\alpha]^{25}D$ dioxane +43°; infrared spectrum shows typical 20β, 25L-bands,[4c] 985(s), 920(s). 905(s), 870(w) cm.$^{-1}$. *Anal.* Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 81.13; H, 11.33. Brief treatment of IX with refluxing methanolic hydrochloric acid gave desoxysarsasapogenin.

20-Isodesoxysmilagenin (20β,22a,25D-Spirostane) (X).—In a similar manner 0.25 g. of 20-isosmilagenone gave 0.085 g., needles from methanol, m.p. 126–127°, $[\alpha]^{25}D$ dioxane −58°, infrared spectrum shows typical 20α,25D-bands, 970(s), 922(s), 896(s), 785(w). *Anal.* Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.78; H, 11.17. Hydrochloric acid reflux of X gave desoxysmilagenin.

20-Isodesoxytigogenin (5a-20β,22a,25D-Spirostane) (XI).—XI was obtained as above, plates from methanol, m.p. 155–160°, $[\alpha]^{25}D$ (dioxane) −54°, infrared spectrum showed typical 20β,25D-bands similar to X. Hydrochloric acid reflux gave desoxytigogenin.

16,22-Epoxy-20(22)-cholestene (XII).—Two grams of 20-isotigogenin in pyridine solution was treated with tosyl chloride as described previously. After the usual ether work-up, $LiAlH_4$ reduction gave a product with infrared

(16) R. E. Marker and E. Rohrmann, THIS JOURNAL, **61**, 943 (1939).

(17) R. E. Marker, T. Tsukamoto and D. L. Turner, *ibid.*, **62**, 2525 (1940).

spectrum showing hydroxyl and tosylate bands absent and disappearance of characteristic spiroketal bands. A peak was present at 1686 cm.$^{-1}$, characteristic of —C=C—O—C— linkages.[18a,b]

20-Isodesoxydiosgenin (5-20β,22a,25D-Spirostene) (XIII).—A mixture of 2.5 g. desoxydiosgenin, 0.7 g. of pyridine hydrochloride and 12 ml. of acetic anhydride was refluxed for 6 hours. Following the usual ether work-up, the residue was refluxed 0.5 hour in 10% methanolic potassium hydroxide to give pseudodesoxydiosgenin. The latter was taken up in methanol and an equal volume of glacial acetic acid was added. After standing overnight, the usual ether work-up gave 0.6 g. of XIII, plates from methanol, m.p. 160–163°, $[\alpha]^{25}D$ dioxane −110°; infrared spectrum similar to X and XI plus additional unsaturation peak at 835 cm.$^{-1}$. *Anal.* Calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.14; H, 10.64. Hydrochloric acid reflux of XIII gave desoxydiosgenin.

20-Isodesoxyyamogenin (5-20β,22b,25L-Spirostene) (XIV).—In the same manner as described under XIII, desoxyyamogenin was converted to XIV as plates from acetone, m.p. 184–186°, $[\alpha]^{25}D$ dioxane −12.3°, infrared spectrum similar to IX plus additional unsaturation peak at 838 cm.$^{-1}$. *Anal.* Calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.39; H, 10.70. Treatment of XIV with hydrochloric acid gave desoxyyamogenin.

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(18) (a) H. Rosenkrantz and M. Gut, *Helv. Chim. Acta*, **36**, 1000 (1953); (b) Hayden, *et al.*, ref. 14.